Cardiac Interleukin-6 in Ischemic Myocardium

To the Editor:

We read with great interest the recent report of Gwechenberger et al. demonstrating that cardiac myocytes in the viable border zone of myocardial infarction exhibited reperfusion-dependent expression of interleukin (IL)-6 mRNA within 1 hour in a canine model of ischemia and reperfusion. These authors point to the first direct histological demonstration of IL-6 mRNA, and they suggest the enhanced expression of IL-6 may exert primary effects on myocardial function, such as reduced contractility, positive protein balance (hypertrophy), and anti-apoptosis. We agree with their hypothesis, but this is not the first demonstration of IL-6 expression in the infarcted heart in vivo.

In our report, we demonstrated that IL-6 protein was immunohistochemically expressed in the hypertrophied myocardium of patients who died 1 to 7 days after myocardial infarction. The greatest expression of IL-6 was confirmed in the adjacent myocardium in patients who died 3 to 4 days after the onset (2.7 ± 0.7), compared with those who died within 1 to 2 days (1.0 ± 0.3). The diameter of IL-6-positive myocytes was significantly increased in patients who died within 1 to 2 days (1.6 ± 0.2), 3 to 4 days (1.8 ± 0.3), or 5 to 8 days (2.0 ± 0.2) after the onset of myocardial infarction. Moreover, the IL-6-positive myocytes were adjacent to the infarcted area, such as in the border zone, and coexpressed with atrial natriuretic peptide (ANP). Our study demonstrated that ischemic myocytes surrounding infarcted myocardium definitely expressed IL-6 proteins in their cytoplasm in the first 7 days after infarction.

Although a link between IL-6 and ANP is not clear, ANP is induced within ventricular myocytes in response to pressure overload, cardiomyopathy, and cardiac hypertrophy. ANP is also considered a genetic marker for in vivo cardiac hypertrophy. These reports suggest that demonstration of IL-6 protein and mRNA in ischemic myocytes surrounding infarcted myocardium may induce cardiac hypertrophy not only in an animal model but also in patients with acute myocardial infarction. These data expand the findings of Gwechenberger et al. and emphasize that cardiac myocytes in the border zone of myocardial infarction produce IL-6, the key element in myocardial adaptation.

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Response

We are delighted to know of the work of Professors Kanda, Kobayashi, and Nagai. We apologize for not having found this reference; we certainly would have referred to it. The fact that this observation has been made in clinical myocardial infarction encourages us to think that our observations are clinically pertinent. We also wish to point out that similar observations were made in a rat model of myocardial infarction in an article published in this journal earlier this year, in which the authors demonstrated induction in the myocyte of both interleukin (IL)-6 and IL-6 receptors utilizing immunohistochemistry with monoclonal antibodies to the proteins.

We included the suggestion that IL-6 might also induce cardiac hypertrophy in the viable border zone surrounding a myocardial infarction as a speculation. We emphasize that early induction of IL-6 in cardiac myocytes was observed only in reperfused myocardial infarctions and was not seen in the absence of reperfusion. Although the induction of IL-6 might well occur in the absence of reperfusion under certain circumstances, we were unable to demonstrate it in our model despite the fact that dogs are known to have very significant collateral circulation. Hypertrophy occurring after myocyte loss is probably primarily related to the increased hemodynamic load on the remaining viable myocardium and is not dependent on reperfusion.

A more specific protective mechanism is likely to be related to the antiapoptotic effects of IL-6 and its related cytokines. The rapid induction of these cytokines early on reperfusion allows their presence during a time period when such an action might be beneficial. The antiapoptotic effects of IL-6–related cytokines were discussed in our article, and we continue to pursue this possibility.

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_Circulation_. 2000;101:e86
doi: 10.1161/01.CIR.101.8.e86
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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